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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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BACON & THOMAS PLLC
625 SLATERS LANE
4TH FLOOR
ALEXANDRIA, VA 223141176

EXAMINER
HINES, JANA A

ART UNIT	PAPER NUMBER
1645	19

DATE MAILED: 12/03/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/417,226	SUNDREHAGEN ET AL	
	Examiner	Art Unit	
	Ja-Na A Hines	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 September 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-7,9-12,16-18,20,25-33,35,36,42-44 and 47-53* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-7,9-12,16-18,20,25-33,35,36,42-44 and 47-53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Amendment Entry

1. The amendment filed September 16, 2002 was entered. The examiner acknowledges the amendment to the specification. Claims 1, 3-5, 9-12, 16, 25-27, 31, 35-36, 42, 44, 47, 49 and 50 have been amended. Claims 19 and 24 have been cancelled. Claims 51-53 have been newly added. Claims 1, 3-7, 9-12, 16-18, 20, 25-33, 35-36, 42-44, 47-53 are under consideration in this office action.

Withdrawal of Rejections

2. The following rejections have been withdrawn in view of applicant's amendments and arguments:

a) The rejection of claims 1, 3-7, 9-12, 16-20, 24-33, 35-36, 42-44, 47-50 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of applicants amendments and arguments.

Response to Arguments

3. Applicant's arguments filed September 16, 2002 have been fully considered but they are not persuasive.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. The rejection of claims 1, 3-7, 9-12, 16-20, 24-33, 35-36, 42-44 and 47-53 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is maintained for reasons already of record. The rejection was based upon the claims reciting new matter.

The claims now recite a volume of liquid so reduced in comparison with the volume of said cell free sample, to provide a cobalamin containing liquid having a cobalamin concentration at least 3 times the holo-TCII concentration in said cell free sample and determining the holo-TCII content in said sample by measuring the amount of cobalamin or TCII-protein in said cobalamin containing liquid arising from the bound holo-TCII.

Applicants refer to figure 3, an explanation supplied by applicant to exemplify the method, is not support for the amendment. However it is noted that this figure is not part of the instantly filed specification. In amended cases, subject matter not disclosed in the original application is sometimes added and a claim directed thereto. Such a claim is rejected on the ground that it recites elements without support in the original disclosure under 35 U.S.C. 112, first paragraph, Waldemar Link, GmbH & Co. v. Osteonics Corp. 32 F.3d 556, 559, 31 USPQ2d 1855, 1857 (Fed. Cir. 1994); In re Rasmussen, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981). See MPEP § 2163.06 - §

2163.07(b) for a discussion of the relationship of new matter to 35 U.S.C. 112, first paragraph. New matter includes not only the addition of wholly unsupported subject matter, but may also include adding specific percentages or compounds after a broader original disclosure, or even the omission of a step from a method. See MPEP § 608.04 to § 608.04(c).

However there is still no support for the amendment. The specification fails to disclose such a volume. Applicant has failed to cite page and line number of the specification as support for the amendment. It appears that there is no teaching of the recited limitation, and the amendment contains new matter, therefore it is rejected.

Instead applicant points to a picture filed in a previous response as support, however this is not adequate support. Moreover, applicant argues that the term is clearly an inherent part if the original disclosure because it would be evident to a skilled worker. However, as applicants argue if the concentration is to be 3-fold greater, the volume must decrease by the same ratio, however the necessary ratio is not inherent. One of skilled art would have to de novo decide what ratio should be attained. This is not an inherent part of the original specification, since applicant later claims that achieving said ratio is a novel step in the method. This argument is not persuasive.

5. The rejection of claims 1, 3-7, 9-12, 16-20, 24-33, 35-36, 42-44 and 47-53 under 35 U.S.C. 112, first paragraph, because the specification is maintained for reasons already of record. The rejection was on the grounds that while being enabling for specific binding ligands which bind TC II such as an anti-TC II antibody or anti-TC

antibody fragment, does not reasonably provide enablement for a specific binding ligand such as polypeptides, oligopeptide, small organic chemical, binders from combinatorial chemistry libraries or phage display library or specifically binding sequences of DNA and RNA since the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Applicants broadly argue that equivalent binding of other ligands exist because binding of antibodies is known in the art and that only suitable testing is necessary to identify potential binders.

However, the specification fails to teach making specific binding ligands such as like polypeptide, oligopeptide, small organic chemical, binders from combinatorial chemistry libraries or phage display library or specifically binding sequences of DNA and RNA that only bind to TCII. Applicants argue that complimentary patterns of charge and topology all necessary to determine binding, yet the specification fails to teach specific complimentary patterns. There is no disclosure of peptides, small organic chemicals or sequences that preferentially bind TC II. Absent factual evidence that the recited ligands will bind TC II; it is not deemed reasonable that one skilled in the art would know how the claimed ligands would bind to TC II. The specification broadly recites a range of binding ligands without any specificity to TCII when the suspension is used for targeting selected cells or tissues the microdevices should contain molecules effective to bind the markers carried on the surface of the target cells (page 8 para. 3).

Therefore, the specification fails to teach examples of the recited specific binding ligands.

Applicants argue that antibodies and antibody fragments can be made. However it is noted that applicants claims encompass more than antibodies and associated fragments, therefore the rejection is maintained because the specification fails to teach specific binding markers and the fact that antibodies are one example of enabled binders does not enable the entire recited components as claimed. In view of the absence of further guidance from Applicants, the skilled artisan would have to discover to specific binding regions for each and every named specific binding ligand. Such experimentation requires ingenuity beyond that expected of one of ordinary skill in the art. Thus non-routine experimentation demonstrates that the specification is not enabled for specifically binding ligands. Therefore, one skilled in the art could not make and/or use the invention as claimed and the rejection is maintained; as applicants' arguments are not persuasive.

6. The rejection of claims 1, 3-7, 9-12, 16-20, 24-33, 35-36, 42-44, 47-53 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is maintained.

Applicants argue that the amendment obviates the rejection. However, if applicant is attempting to say that the holo-TCII the same as cobalamin content or TCII protein then the terms need to remain consistent throughout the claims.

It is noted that page 10 of the instant response refers to holo-TCII as a 1:1 complex of cobalamin and TCII protein. If this is true than how can a cobalamin containing liquid have a cobalamin concentration at least 3 times the holo-TCII concentration? Clarification is requested.

Moreover, the claim is confusing since the method does not teach where the cobalamin is coming from since its concentration is 3 times greater than holo-TCII. There is no recitation of releasing the TCII-protein, therefore it is unclear where this protein comes from. Therefore the claim is still unclear as to where, how and what steps will allow the determination of holo-TCII to occur.

Applicant urges that the claims do not lack a correlation step that correlates the determination of holo-transcobalamin II (holo-TCII) and determining the cobalamin content by measuring the cobalamin or the TCII –protein content arising from the holo-TCII released from the specific binding ligand. Applicant must positively recite necessary method steps. Stating that a measurement of cobalamin or TCII protein arising from the holo-TCLL released from the specific binding ligand is not a sufficiently positively recited method step. Thus the rejection is maintained.

Applicant has amended claim 25, however it is still unclear how one will know prior to the assay being performed, whether at least 80% of holo-TCII is present within the cell free sample. Clarification is therefore requested.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. The rejection of claims 1, 5, 7, 9, 11, 12, 42-44, 47, 48 and 53 under 35 U.S.C. 102(b) as being anticipated by Herbert et al., US Patent 4,680,273 is maintained.

Applicant argues that this section of the office action is based upon the office action of April 1999, and that the Herbert reference was previously used in a 103 rejection. However, it is noted that the reference has been applied to claims in different rejections because the claims have been amended four times. Therefore, applicants' argument that it is difficult to address the rejection should be viewed in light of the fact that the method steps of the instant claims keeps being amended.

Applicant argues that Herbert is not known to bind all of the TCII in a sample and take up some of the HC. However, applicant previously stated that holo-TCII, cobalamin and TCII are all equivalent proteins, thus if Herbert et al., binds TCII or holo-TCII than Herbert et al., meets the limitations of the claim. Moreover, Herbert et al., teach a separation step as required by the claims. Specifically Herbert et al., teach separation steps include precipitation of TCII, although other methods for separating TCII from a sample are applicable. TCII can be separated from a sample using selective antibodies where the antibody can be coupled to a solid support to more easily separate TCII. At pH=6, TCII binds to sephadex while the other transcobalamin proteins do not. Therefore, Herbert et al., meets the limitations of the claims and applicants' arguments that Herbert et al., binders are not good enough are not persuasive since there are no requirements regarding binding recited in the instant claims.

Applicants' arguments drawn toward the expensive of Herbert et al., antibodies is unpersuasive, since applicant's claims also support the use of antibodies as specific binders.

Applicant argues that Herbert et al., could not reliably detect cobalamin at a specific level. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., detection of serum levels below 200pM) are not recited in the rejected claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). It is noted that Herbert et al., meets the limitations of the claims by teaching the same method steps as instantly claimed. Therefore applicants' arguments are not persuasive.

Applicants argue that Herbert et al., teach away from a method using specific binding ligands, however Herbert et al., teach that in an immunoassay the binder can be

a monoclonal or polyclonal antibody, a tracer is also used which can be vitamin B_{12} or an appropriate analog that is labeled with a detectable marker. Therefore, Herbert et al., teach specific binding ligands.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. The rejection of claims 3,16,17, 24-26 and 35-36 under 35 U.S.C. 103(a) as being unpatentable over Herbert et al., US Patent 4,680,273 in view of Houts et al., US Patent 4,465,775 is maintained for reasons already of record.

Applicant again argues that there is no indication that the detailed responses have been considered. However, it is noted that in view of the new grounds of rejection supplied in the office action of March 12, 2002, applicants' thrice-amended claims were fully considered and prior art was accordingly supplied.

Applicants argue that the proteins of Houts cannot be cobalamin analogues. However, it is noted that the specification fails to define cobalamin analogues. There is no support in the specification that the analogues of Houts et al., do not meet the limitation of the claims. Applicants' mere argument that the proteins are not analogues is not persuasive.

In response to applicants' arguments that no concentration steps are taught, it is noted that no more than routine skill is involved in adjusting the amount of a component of a claimed process as stated in the claims. The cited references teach a separation step and steps that release to previously bound cobalamin into a concentrated environment. Therefore, neither changes in concentrations nor determining optimum concentrations that are suitable for materials have been held to involve patentable inventions.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, it would have been obvious at the time of applicants invention to use the antibodies to transcobalamin II in a competitive sandwich ELISA assay on a solid support as taught by Houts, in the method of determining the cobalamin content in a sample as taught by Herbert , because Houts teaches a modified method of assaying TCII or any cobalamin analogues using samples from human plasma or serum, where a centrifuge step is performed and cyanocobalamin in either a direct or indirect assay can be assayed with any one of a variety of detectable signals that can indicate presence using immobilized and non-immobilized ligands.

9. The rejection of claims 6-7, 12, and 8-20 under 35 U.S.C. 103(a) as being unpatentable over Herbert et al., and Houts as applied to claims 1,5 and 16 above further in view of McLean et al.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, one skilled in the art would have expected a reasonable level of success by including monoclonal antibodies specific for apo and holo transcobalamin and known to be associated with biotin and avidin as taught by McLean et al., with the assay methods for the determination of TCII bound cobalamin sample comprising contacting a sample body fluid with an immobilized specific binding ligand like a antibody specific for TCII, separating the bound fraction from the unbound fraction and measuring the amount of TCII bound cobalamin obtained as taught by Herbert et al., in view of Houts because McLean et al., teach that no more than routine skill is required to incorporate a monoclonal antibody specific for the apo or holo TCII ligand which can detect or immunoprecipitate TCII in serum.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies

(i.e., the issue that highly specific binders can be used to provide a simultaneous separation and concentration step which allows the level of holo-TCII to be measured) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

It is noted that McLean et al., teach monoclonal antibodies specific for apo and holo transcobalamin and known to be associated with biotin and avidin and that McLean et al., teach that no more than routine skill is required to incorporate a monoclonal antibody specific for the apo or holo TCII ligand which can detect or immunoprecipitate TCII in serum. Therefore, applicants argument that the publication could not be read to provide the instant assay is not persuasive since, one of ordinary skill in the art would have a reasonable level of success by including monoclonal antibodies specific for apo and holo transcobalamin and known to be associated with biotin and avidin as taught by McLean et al., with the assay methods for the determination of TCII bound cobalamin sample comprising contacting a sample body fluid with an immobilized specific binding ligand like a antibody specific for TCII, separating the bound fraction from the unbound fraction and measuring the amount of TCII bound cobalamin obtained as taught by Herbert et al., in view of Houts.

10. The rejection of claims 4 and 49 under 35 U.S.C. 103(a) as being unpatentable over Herbert et al., in view of Houts and further in view of Allen et al., (US Patent 5,374,560) is maintained for reasons already of record.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. In this case, it would have been obvious to automate the method as taught by Allen e al., in the method of determination as taught by Herbert et al., in view of Houts, because Allen et al., shows it to be conventional and well known to automate assays to detect cobalamin. Furthermore, it has been held that broadly providing a mechanical or automatic assay to replace manual activity that has accomplished the same results involves only routine skill in the art.

11. The rejection of claims 27-33 under 35 U.S.C. 103(a) as being unpatentable over Herbert et al., and McLean et al, as applied to claims 1 above further in view of Hoyle et al is maintained for reasons already of record.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. In this case, no more than routine skill would have been required to incorporate monoclonal antibodies of McLean et al, with high affinity constants as taught by Hoyle et

al., into the assay of Herbert et al., because Hoyle et al., teach it would have been obvious at the time of applicants invention to use antibodies with the high affinity constants because they provide for a more sensitive immunoassay.

Conclusion

12. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ja-Na Hines whose telephone number is (703) 305-0487. The examiner can normally be reached on Monday through Thursday from 6:30am to 4:00pm. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Ja-Na Hines
November 27, 2002

MARK NAVARRO
PRIMARY EXAMINER